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(54) **MACROCYCLES USEFUL IN THE TREATMENT OF ALZHEIMER'S DISEASE**

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(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**

C07D 273/02	(2006.01)
C07D 291/08	(2006.01)
C07D 413/04	(2006.01)
C07D 413/12	(2006.01)
C07D 498/08	(2006.01)

(52) **U.S. Cl.** **514/183**; 540/456

(58) **Field of Classification Search** 514/183; 540/456

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,043,357 A 3/2000 Abbenante et al.

FOREIGN PATENT DOCUMENTS

WO WO 96/16950 6/1996

OTHER PUBLICATIONS

J. Med. Chem. 2000, 43, 1271–1281.

Proc. Natl. Acad. Sci, Vol. 87, pp. 8805–8809, Nov. 1990, Swain et al.

J. Am. Chem. Soc., Vol. 117, pp. 10220–10226, Oct. 1995/ Abbenante et al.

J. Med. Chem. 2000, 43, 3495–3504 Tyndall et al.

J. Med. Chem. 2002, 45 (2). 371–381 Glenn et al.

Current Medicinal Chemistry, 2001, 8(8), 893–907 Tyndall et al.

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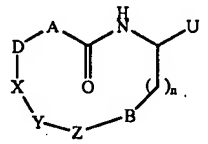
(57) **ABSTRACT**

The present invention is macrocycles of the formula (X):

(X)



for treating Alzheimer's disease and other similar diseases. These compounds include inhibitors of the beta-secretase enzyme for the treatment of Alzheimer's disease and other diseases characterized by deposition of A beta peptide in a mammal. The compounds of the invention are useful in pharmaceutical compositions and methods of treatment to reduce A beta peptide formation.

35 Claims, No Drawings

MACROCYCLES USEFUL IN THE TREATMENT OF ALZHEIMER'S DISEASE

This application claims the benefit of U.S. Provisional Patent Application Nos. 60/297,505 filed Jun. 12, 2001, and 60/333,082 filed Nov. 19, 2001.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to substituted cyclic amides and such compounds that are useful for the treatment of Alzheimer's disease. More specifically, the invention relates to such compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce amyloid beta peptide (A beta), a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

2. Description of the Related Art

Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgment, and orientation. As the disease progresses, motor, sensory, and linguistic abilities are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

Alzheimer's disease is characterized by two major pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment know as A beta. Individuals with AD exhibit characteristic beta-amyloid deposits in the brain (beta amyloid plaques) and in cerebral blood vessels (beta amyloid angiopathy) as well as neurofibrillary tangles. Neurofibrillary tangles occur not only in Alzheimer's disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurodegenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition of A beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39–42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Pat. Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin. See, for example, Sindha et al., 1999, *Nature* 402:537–554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A beta) plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. See, for example, Seubert et al., 1992, *Nature* 359:325–327.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. In vivo processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1–19.

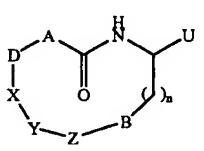
BACE1 knockout mice fail to produce A beta, and present a normal phenotype. When crossed with transgenic mice that over express APP, the progeny show reduced amounts of A beta in brain extracts as compared with control animals (Luo et al., 2001 *Nature Neuroscience* 4:231–232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A beta in the brain provides a therapeutic method for the treatment of AD and other beta amyloid disorders.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are effective inhibitors of A beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

SUMMARY OF THE INVENTION

The invention provides compounds of formula (X):



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